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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/606,909
Filing Date: June 29, 2000
Appellant(s): PETTIS ET AL.

Laura Coruzzi
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 7/31/2009 appealing from the Office action mailed 9/23/2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows:

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner. The double patenting rejections of the claims over the claims of Applications 10/868,482; 10/867,908; 10/487,485; 11/004,780; 10/841,992; 10/803,735; 10/650,039; 10/429,973; and 09/893,746 are withdrawn as Applications 10/867,908; 10/487,485; 11/004,780; 10/841,992; 10/803,735; 10/650,039; and 09/893,746 have been abandoned and the previously applied claims of Applications 10/868,482 and 10/429,973 have been cancelled and the new claims pending in these Applications no longer conflict with the claims of the present application.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,848,991	GROSS ET AL	12-1998
5,807,375	GROSS ET AL	9-1998
6,611,707	PRAUSNITZ ET AL	8-2003
6,007,821	SRIVASTAVA ET AL	12-1999
6,056,716	D'ANTONIO ET AL	5-2000

Puri et al. "An investigation of the intradermal route as an effective means of immunization for microparticulate vaccine delivery systems" Vaccine 18, pp. 2600-2612

"The Merck Manual of Diagnosis and Therapy" 1999, 17th Edition, Beers & Berkow, ed., Merck Research Laboratories, Devision of Merck & Co., Inc., Whitehouse Station, NJ, pp. 2559-2567

Autret et al. "Comparison of the plasmatic concentration and the tolerance of a single dose of human calcitonin following intradermal and subcutaneous administration," Therapie 46, 5-8

The diagram submitted on page 11 on the Appeal Brief has not been relied on as evidence. MPEP § 1205 states “a brief shall not include any new or non-admitted amendment, or any new or non-admitted affidavit or other evidence.” The diagram which Appellant has included had not previously been presented. As reference to unentered evidence is not permitted in the brief, Appellant’s arguments as to the diagram have not been considered. Any new evidence which the Appellant wishes to rely on or have considered by the Examiner must be submitted pursuant to §§ 1.130, 1.131, or 1.132.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 2-4, 10-13, 15, 16, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over GROSS (US 5,848,991) OR GROSS (US 5,807,375) in view of PRAUSNITZ (US 6,611,707), AUTRET ("Comparison of the plasmatic concentration and the tolerance of a single dose of human calcitonin following intradermal and subcutaneous administration"), PURI ("An investigation of the intradermal route as an effective means of immunization for microparticulate vaccine delivery systems"), D'Antonio et al (US 6,056,716), SRIVASTAVA (US 6,007,821), and The Merck Manual of Diagnosis and Therapy (17th ed. 1999).

Gross '991 discloses a method of delivering various drugs, particularly insulin and hormones, intradermally (column 3, lines 40-41; column 6, line 56 – column 7, line 20) using a single needle having a length from the housing of 0.3mm – 3mm (column 4, lines 10-35). This length would put the needle outlet at a depth within the range of about 0.25mm - 2mm or 0.75mm - 1.5mm when the housing is set against a patient's skin to achieve ID delivery. Additionally, this depth would be required to meet the disclosure of Gross '991 to deliver the drugs intradermally. Gross '375 discloses a method of drug delivery using a needle that extends into the intradermal layer to deliver insulin into this intradermal layer (column 5, line 25 - column 6, line 34; column 10, 1ines 24-30; column 14, lines 40-62). The needle length is chosen from the range 0.3mm - 3mm that extends from the housing to deliver into the intradermal layer at a depth of about 0.25mm - 2mm or 0.75mm - 1.5mm.

Gross '991 and Gross '375 are silent with respect to the needle outlet exposed height of 0- 1 mm and the pharmacokinetic profile of the ID delivered drugs. Prausnitz teaches the use of needles with zero exposed height to deliver drugs into the skin (column 3, 1ines 27-38). It would have been obvious to one of ordinary skill in the art at the time of the invention to use the teachings of Prausnitz in the method of Gross '991 or Gross '375 in order to provide a known flow dynamic as desired from the end of the

delivery needle. The zero exposed height needle as disclosed in Prausnitz is known to provide a substantially longitudinally directed flow as opposed to a more pronounced radially directed flow component as found in beveled needles when liquid exits the needle opening. One of ordinary skill in the art would know to select a particular exposed height needle dependent upon the desired flow delivery.

Autret, Puri, D'Antonio, and Srivastava each suggest a greater C_{max} and bioavailability in intradermal injections as compared to subcutaneous injections (see Autret Figure 1; Puri, pages 2609-2610; D'Antonio column 29, lines 3-23; and Srivastava column 19, line 60 – column 20, line 25).

Autret discloses intradermal injection of a hormone resulting in a pharmacokinetic profile similar to subcutaneous delivery, but with a higher plasma level and bioavailability as assessed by C_{max} and T_{max} (Figure 1). The Merck Manual is cited here as evidence showing the various methods that bioavailability is assessed (see pages 2560).

Puri discloses that lower doses can be used with ID delivery than with SC delivery (pages 2610). The ability to use lower doses is the practical result when a higher C_{max} and bioavailability is achieved with equal dosages; whereby the required C_{max} and bioavailability is still achieved to treat the illness. As drug treatment efficacy depends on C_{max} and bioavailability, one of ordinary skill in the art would recognize that when equal ID and SC dosages give higher C_{max} and bioavailability via the ID route, then the ID dosage can be reduced to treat a patient.

D'Antonio discusses experimental evidence in the prior art that indicate ID injections into the dermis are many times more powerful than SC injections. This allows greatly reduced dosages to be used (column 29, lines 3-9). The ability to use lower dosages shows that a higher C_{max} and bioavailability is achieved with ID over SC delivery.

Srivastava describes a method of ID delivery of drug treatments where the ID injections typically required lower dosages than SC delivery (column 20, lines 3-7).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the teachings of Autret, Puri, D'Antonio, OR Srivastava in the drug delivery method of Gross '991 and Prausnitz OR Gross '375 and Prausnitz to deliver effective drug treatments at particular pressures and flow rates to achieve higher C_{max} and bioavailability with intradermal injection as compared to subcutaneous injection in order to effectively treat patients using lower dosages, thereby saving drug costs and inventories. Conserving drug inventories and lowering the costs of drug treatments is desirable in the drug delivery field to maximize the treatment availability of the drug, and is something one of ordinary skill in the art is constantly looking to achieve.

Regarding claim 4, Gross '991 OR Gross '375 does not disclose using multiple needles. Prausnitz teaches using multiple needles to achieve the desired drug injection flow (column 3, line 27 - column 4, line 7). It would have been obvious to one of ordinary skill in the art at the time of the invention to use the teachings of Prausnitz in the method of Gross '991 OR Gross '375 in order to achieve a larger drug delivery area and treatment zone.

Regarding claim 16, Gross '991 OR Gross '375 does not disclose flow control by needle spacing or diameter. Prausnitz teaches using flow control by varying needle diameter or spacing (column 4, 1ines 3-7; column 8, 1ines 54-67). It would have been obvious to one of ordinary skill in the art at the time of the invention to use the teachings of Prausnitz in the method of Gross '991 OR Gross '375 in order to control flow parameters to vary injection rates and effects as desired.

2. Claims 2-4, 10-13, 15, 16, and 29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 31, 32, 36, 37, 39, 49, 67, 73 of copending Application No. 10/028988; and claims 69, 72, 83-86, 88, 90, 100, 103 of copending Application No. 10/028989 in view of Gross '991 or Gross '375, and Prausnitz, Autret, Puri, D'Antonio, and Srivastava. The above listed claims of copending Applications 10/028988 and 10/028989 recite

methods of administering a therapeutic agent into the intradermal compartment to achieve higher bioavailability as compared to another delivery route. These claims do not recite the use of a needle with an exposed height of 0-1 mm to deliver a drug intradermally to achieve higher C_{max} along with higher bioavailability over delivering a drug subcutaneously. Gross '991 and Gross '375 teach a method of delivering insulin and hormones intradermally using a needle in a controlled manner. Prausnitz teaches injecting a drug through multiple needles with a zero exposed height. Autret, Puri, D'Antonio, and Srivastava each disclose achieving a greater C_{max} and bioavailability via intradermal injections as compared to subcutaneous It would have been obvious to one of ordinary skill in the art at the time of the invention to use the teachings of Autret, Purl, D'Antonio, Srivastava, Gross '991, Gross '375, and Prausnitz in the claimed method of the claims Applications 10/028988; and 10/028989 in order to provide a known flow dynamic as desired from the end of delivery needles as a longitudinally directed flow and to effectively treat patients with lower drug costs resulting from using less drugs dosages and maintaining greater drug inventories.

These are provisional obviousness-type double patenting rejections.

(10) Response to Argument

Appellant argues that the prior art does not teach the claimed invention because the references do not teach "parameters which affect the resulting PK profile and dosing accuracy that are critical for proper insulin delivery" (page 11 of the Appeal Brief). The parameters Appellant is referring to are: "needles no more than about 2mm long," "a needle outlet which may be formed by a bevel," and "the needle outlet being placed at a depth of about 250um-2mm when the needle is inserted in the skin, preferably the outlet is at a depth of about 750um-1.5mm, and more preferably at a depth of about 1mm" (page 11 of the Appeal Brief). However, Appellant's arguments contradict that which Appellant has expressly admitted in the specification filed. In the specification, on page 4, lines 3-6, Appellant states "the injection device

used for ID administration according to the invention is not critical as long as it penetrates the skin of a subject to a depth sufficient to penetrate the intradermal space without passing through it. In most cases, the device will penetrate the skin to a depth of about 0.5-3mm, preferably about 1-2mm."

Appellant also argues that the Gross references do not disclose delivery to the ID layer. The Examiner disagrees as the disclosures of both the '991 and '375 Gross patents each provide several references directed to delivery of a drug which is confined to the ID layer. Gross '375 discloses intradermal delivery depending on the condition treated (column 6, lines 25-34), disclosing that "the choice of intradermal OR subcutaneous delivery, however, depends on the condition to be treated;" as well as disclosing that the needle tip is placed intradermally to accomplish the drug delivery (column 5, 1ines 25- 29), stating that "the needle is of a suitable length to penetrate the patient's skin either intradermally (i.e. the tip of the needle extends to a point within the dermis) OR subcutaneously." The Gross '991 reference discloses in column 3, lines 38-40 a device which can be used for delivering drugs to one of three distinct regions: the interface between the epidermis and the dermis, the interior of the dermis (i.e. intradermal compartment), OR subcutaneously. The '991 reference further discloses in column 7, lines 23-51 an intradermal drug delivery device having a needle projecting from a flat surface of 0.3-1.0mm "just sufficient to penetrate through the epidermis of the subject's skin" (thus positioning the needle within the intradermal compartment which is the skin layer located directly underneath the epidermis). It is the Examiner's position that the references which both Gross patents make to delivery the intradermal layer is meant as directly stated: that the delivery results in delivering the drug into the intradermal layer - not outside of this layer - thus requiring the needle outlet to be completely within the intradermal layer. Furthermore, it is the Examiner's position that one of ordinary skill in the art would find obvious that a statement of delivering a drug to a desired location would require the needle outlet (depth and exposed height) to be within the desired location, so as to accomplish the desired delivery. If the needle outlet depth and exposed height were not within the intradermal compartment, and the Gross

patents were describing a delivery to non-selective locations, it is the Examiner's position that Gross would have referred to delivery of the drug being to the 'interface between the epidermis and dermis AND the interior of the dermis AND subcutaneously' rather than referring to the delivery locations in the alternative ('the interface between the epidermis and the dermis, the interior of the dermis, i.e. intradermal compartment, OR subcutaneously').

Though Gross is silent as to the exposed height of the needle, it is the Examiner's position that it would be obvious to one of ordinary skill in the art that if Gross discloses embodiments in which a delivery device is used to deliver a drug to a single layer (such as delivery only to the intradermal layer as discussed above) the exposed height of the needle outlet would be such that it would be limited to a length no greater than the width of that layer, as otherwise the delivery would then not be confined to the interior of only that layer. To this extent, it is the Examiner's position that it would have been obvious to one of ordinary skill in the art to modify the devices of Gross with needles having a zero exposed height as taught by Prausnitz, as delivering a drug using a needle having a zero exposed height would limit the delivery of the drug through the needle to the depth of the outlet of that needle. Although, as pointed out by the Appellant, Prausnitz teaches using microneedles which target the transdermal layer (as opposed to the intradermal layer as taught by both Gross references), it is the teaching of using a zero exposed height needle structure of the Prausnitz reference which is being applied to the Gross reference. It would be obvious to one of ordinary skill in the art that the teaching of such a microneedle structure would be applicable to needles of any length, not just those intended for transdermal applications.

Appellant further argues that the references are silent as to improved pharmacokinetics resulting from intradermal administration. As to the Autret reference, Appellant states that Autret does not recognize a PK profile that exhibits a higher bioavailability. However, Appellant's arguments are misleading as the arguments are based on limitations which are not recited in the claims, are not the same scope of the claims, and furthermore have no support in the application as originally filed. Appellant is

arguing that the claimed limitation 'bioavailability' is meant to be equivalent to AUC (area under the curve). Using this reasoning, Appellant argues that Autret does not disclose a PK profile for intradermal drug delivery which has a greater AUC than that of subcutaneous delivery. However, Examiner points out that the claims recite an ID delivery method exhibiting higher bioavailability – not greater AUC. As disclosed in the Merck Manual (cited above), there are several methods to assess bioavailability besides using AUC, one of which is based on C_{max} and T_{max}. The use of AUC as a measure of bioavailability is not recited in the claims nor is it disclosed explicitly in the application that bioavailability is calculated only by AUC with reference to the disclosed invention. For this reason, it is the Examiner's position that the disclosure of Autret of higher biovailability (as calculated by C_{max} and T_{max}) of drug when administered intradermally as compared to subcutaneous administration teaches the claimed limitation.

Appellant argues that the teachings of Puri, D'Antonio and Srivastava are not relevant in establishing that ID as compared to SC delivery of a drug provides for a PK profile exhibiting a higher C_{max} and higher bioavailability because these references compare ID and SC vaccine delivery. Appellant argues that the efficacy of vaccines is measured by immunological response to the antigen and thus that pharmacokinetic studies are meaningless in the vaccine art. Examiner disagrees. Though the efficacy of vaccines themselves may be measured by immunological response, Examiner points out that both Puri and Srivastava disclose the use of non-vaccine based delivery vehicles which are used to deliver and release the vaccine to the immune system (see Puri, page 2601, left-hand column, the paragraph beginning with "Apart from the administration route" and Srivastava column 190, line 60—column 22, line 40). Thus, while the pharmacokinetic parameters such as C_{max} and bioavailability may not be relevant in gauging the potency of a vaccine, such parameters are relevant in gauging the mechanism of distribution of the pharmaceutically based delivery vehicle. To this extent, both Puri and Srivastava disclose that administration of vaccines attached to a delivery vehicle exhibit improved PK profiles when administered intradermally as compared to subcutaneous injection.

In regards to Appellant's argument that D'Antonio is concerned with injection of vaccines and thus is not relevant to the teaching of PK profiles exhibited by different routes of administration, Examiner points to column 1, lines 53-58 where D'Antonio refers to injecting fluids other than vaccines. Thus, though D'Antonio may disclose the delivery of vaccines as one example of the type of administration the invention may be used for, the teachings of D'Antonio (see column 29, lines 3-9) are also relevant in the comparison of ID delivery to delivery to intramuscular and subcutaneous locations for drugs which display PK profiles.

Based on the evidence presented above, it is the Examiner's position that since the Gross references each disclose methods of intradermal delivery of insulin which meet the limitations of the Appellant's claimed invention, it is inherent that practicing the methods of the Gross references would also result in PK profiles exhibiting higher C_{max} and higher bioavailability as compared to subcutaneous delivery. As further support for this position, Examiner points to the teachings of Autret, Puri, D'Antonio, and Srivastava, all of which recognize the pharmacokinetic benefits of intradermal as opposed to subcutaneous delivery of various drugs.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Catherine N Witczak/

Examiner, Art Unit 3767

Conferees:

/Kevin C. Sirmons/

Supervisory Patent Examiner, Art Unit 3767

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TQAS, TC 3700